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(54) Title: THE PROCESS OF MANUFACTURING PHARMACEUTICAL GRADE TANNATES

(57) Abstract: Antihistamines are available in the form of fee bases as well as salt i.e. hydrochloride, maleate, tannate, etc. Frequently, it is necessary to utilise antihistamines in the form of tannate salt because such salts are generally quite stable and may be administered in such from without untoward side effects. Tannic acid, also known as tannin, is a well know naturally occurring substance. Tannic acid, which is available commercially, usually contain about 5 % of water, has a molecular weight of about 1700 and is typically produced from Turkish or Chinese nutgall. Antihistamine tannates, presently manufactured commercially, are relatively impure. Such tannates are prepared by the reaction of antihistamine free base with tannic acid and using a volatile solvent, isopropanol (IPA). The yield is only fair (around 70 %) and decomposition products e.g. 2-5 % along with significant amount of volatile solvent, isopropanol (6-10 %) remains with the product, which cannot be removed. According to present invention, the tannates are made by dissolving tannic acid and amine in different compatible solvents. The solvents can be halogenated alkanes or alkanoic esters. The examples of halogenated alkane is chloroform, and that of alkanoic ester is ethyl acetate. This avoids the use of isopropanol. This method gives tannates which are lighter in colour. Ephedrine and Pseudoephredine tannates are prepared by using ethyl acetate as a medium for reactions to get pharmaceutical grade tannate.

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1. THE PROCESS OF MANUFACTURING PHARMACEUTICAL GRADE TANNATES

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3. The following specification particularly describes and ascertains the nature of this invention and the manner in which it has to be performed.

FIELD OF THE INVENTION

The objective of the present invention is to manufacture pharmaceutical grade tannates without the use of isopropanol (IPA).

The further objective of the present invention is to manufacture pharmaceutical grade tannates, using mixture of solvents.

The further objective of present invention is to improve the yield of pharmaceutical grade tannates.

BACKGROUND OF THE INVENTION

Antihistamines are available in the form of free bases as well as salts i.e hydrochloride, maleate, tannate etc. Frequently, it is necessary to utilise antihistamines in the form of tannate salt because such salts are generally quite stable and may be administered in such from without untoward side effects. Tannic acid, also known as tannin, is a well known naturally occurring substance. Tannic acid, which is available commercially, usually contain about 5% of water, has a molecular weight of about 1700 and is typically produced from Turkish or Chinese nutgall.

Antihistamine tannates, presently manufactured commercially, are relatively impure. Such tannates are prepared by the reaction of antihistamine free base with tannic acid and using a volatile solvent, isopropanol (IPA). The yield is only fair (around 70%) and decomposition products e.g 2-5% along with significant amount of volatile solvent, isopropanol (6-10%) remains with the product, which cannot be removed. As per guidelines for pharmaceutical agents, the residual solvents should be less than 0.5% or 5000 ppm.

Many antihistamine tannates are heat sensitive e.g. phenyleherine tannates and therefore undergo decomposition quite readily upon prolonged exposures to temperatures as low as 50°C. Accordingly, even if the solvent utilized in its preparation has relatively high vapour pressure e.g. as in isopropanol, it is impossible to reduce the solvent content below 6% based on the weight of antihistamine tannate even at reduced pressures and very mild elevated temperatures. Morever from environment point of view, it would be desirable if antihistamine tannates would be manufactured such that use of volatile solvents like isopropanol would be avoided.

US patent 5663415 describes a method by treating the antihistamine tannate in isopropanol with tannic acid in isopropanol at 60-80°C for 1-2 hours. The resulting antihistamine tannate has isopropanol 8-10% and cannot be removed on prolonged heating under vacumn.

Similarly, in US patent 5599846, phenyleherine tannate was synthesized by isopropanol route. The resulting antihistamine tannate had isopropanol 8% and 2% degradation products.

REFERENCES:

1. U.S. Patent No. 5663415.
Process for preparing antihistamine tannates.
Chopdekar VM et al.
Jame Fine Chemicals, Inc.

2. US Patent no. 5599846.
Phenylehedrine tannates composition.
Chopdekar VM et al.
Jame Fine Chemicals, Inc.

SUMMARY OF THE INVENTION

It has now been found that it is possible to avoid the use of isopropanol during the manufacture of pharmaceutical grade tannates. This is possible by using compatible solvents like halogenated alkanes or alkanoic esters.

According to the present invention, the method gives tannates which are lighter in colour.

DESCRIPTION OF THE INVENTION

According to the present invention is described a method to manufacture pharmaceutical grade tannates, using mixture of compatible solvents.

Chloroform or ethyl acetate is charged. Tannate base is added to this chloroform. Tannic acid solution is prepared by dissolving in ethyl acetate. The above Tannic acid prepared is added into Tannate base solution. The solution is stirred for 3 hours at 40-45°C. This is then cooled to 20-25°C. The material is centrifuged and washed with hexane. The material is then unloaded. The product is dried.

EXAMPLE 1- EPHEDRINE TANNATE:

| | |
|---|---|
| Ethyl acetate : | 330 ml |
| Ephedrine base: | 10 gms |
| Tannic acid: | 20 gms in 230 ml ethyl acetate |
| Hexane: | 800 ml |

330 ml of chloroform is charged to which 10 gms base is added. Tannic acid is prepared by dissolving 20 gms in 230 ml ethyl acetate; which is then added to base solution. The solution is stirred for 3 hours, cooled and filtered. This then washed with hexane and dried.

The above tannate prepared reveals the following with the yield of 23 gms:

1. Description: Yellowish tan, fine powder
2. Water content: 5.69% w/w
3. Residue on Ignition: 0.33% w/w
4. Heavy metals: Less than 5 ppm
5. Tannic acid: 64.30% w/w
6. Ephedrine base: 30.44% w/w
7. Assay: 99.43% w/w
8. Residual solvents: Ethyl acetate: 2613 ppm

EXAMPLE 2- PSEUDOEPHEDRINE TANNATE

| | |
|---|---|
| Ethyl acetate: | 500 ml |
| Pseudoephedrine base: | 10 gms |
| Tannic acid: | 21.4 gms in 400ml ethyl acetate |
| Hexane: | 300 ml |

500 ml of ethyl acetate is charged to which 10 gms base is added. Tannic acid is prepared by dissolving 21.4 gms in 400 ml ethyl acetate, which is then added to base solution. The solution is stirred for 3 hours, cooled and filtered. This then washed with hexane and dried.

The above tannate prepared revealed the following, with a yield of 23 gms:

1. Description: Cream powder
2. Water: 4.33% w/w
3. Residue on Ignition: 0.23% w/w
4. Heavy metals: less than 5 ppm
5. Tannic acid: 63.35% w/w
6. Pseudoephedrine base: 32.33% w/w
7. Assay: 100.1% w/w
8. Residual solvent: Ethyl acetate: 1251 ppm

EXAMPLE 3- CARBETAPENTANE TANNATE

| | |
|---|---|
| Chloroform: | 840 ml |
| Carbetapentane base: | 50 gms |
| Tannic acid: | 75 gms in 920 ml ethyl acetate |
| Hexane: | 800 ml |

840 ml of chloroform is charged to which 50 gms base is added. Tannic acid is prepared by dissolving 75 gms in 920 ml ethyl acetate, which is then added to base solution. The solution is stirred for 3 hours, cooled and filtered. This then washed with hexane and dried.

The above tannate prepared reveals the following, with a yield of 100 gms:

1. Description: Pale yellow, tan, fine powder
2. Water: 1.62% w/w
3. Residue on Ignition: 0.12% w/w
4. Heavy metals: Less than 5 ppm

5. Tannic acid: 61.98% w/w
6. Carbetpentane base: 36.12% w/w
7. Assay: 99.72% w/w
8. Residual solvents: a) Chloroform: Nil
   b) Ethyl acetate: 157.5 ppm

We claim:

1. The process for manufacturing pharmaceutical grade tannates, wherein
   a) Suitable compatible solvent is charged.
   b) Tannate base is added to this solvent.
   c) Tannic acid solution is prepared by dissolving in a compatible solvent.
   d) The above Tannic acid prepared is added into Tannate base solution.
   e) The solution as in (d) is stirred for a period of time at the said maximum temperature and then cooled.
   f) The material is centrifuged and washed with a volatile organic solvent.
   g) The material is then unloaded and dried.

2. The process, as claimed in claim 1 wherein the tannate base is selected from the group consisting of phenylephrine, carbetapentane, pyrilamine, chlorpheniramine, ephedrine, pseudoephedrine, brompheniramine, bromodiphenhydramine, diphenhydramine, pheniramine, Phenyltoxamine, clemastine, tripelennamine, cyproheptadine, phenindamine and phenyltoloxamine as a single ingredient or a combination of more than one.

3. The process, as claimed in claim 1 and 2 wherein the tannate base is Ephedrine.

4. The process, as claimed in claim 1 and 2, wherein the tannate base is Pseudoephedrine.

5. The process, as claimed in claim 1 and 2 wherein the tannate base is Carbetapentane.